

REMARKS

INTERVIEW SUMMARY

Applicant's agent telephoned the Examiner on February 4, 2009, and sought clarification with regard to objection 4 and 5d in the Office Action of 11/04/2008. Agent believes the submissions made today address the Examiner's concerns.

STATUS OF THE CLAIMS

2. Claims 16-21 were cancelled in a previous response. Claims 2 and 6 have been cancelled in this response. New claims 22-24 have been added. Claims 22 and 23 derive support from pages 10 and 11 of the description and original claims 4 and 5. Claim 24 derives support from former claim 11. Claims 12-14 have been withdrawn as being directed to a non-elected species. Claims 1, 3-5, 7-15, and 22-24 are pending in this application.

UNITY OF INVENTION

3. Claims 12-14 have been withdrawn and amended. It is submitted that the claims as amended do not represent a different species.

35 USC 112

4. The Examiner finds that claims 1-11 and 15 lack enablement. This objection appears to have been raised, at least in part, for failure to provide units for T_k , T_m , and t_h . Units have now been indicated in the claims for all these terms at their first introduction.

The Applicant has sought clarification from the Examiner by telephone on February 4 as to the meaning of the statements that "the formula apparently does not express any advancement in the art" and "no known evidence in the field that the apparently new formula has any patentable reliability in the field". It is the applicant's understanding that the Examiner finds that the formula lacks support in the description and that the Examiner is unsure of the origin of this formula.

This formula, relating the culturing temperature, the conditioning temperature, and the conditioning time, has been derived by the Applicant, and is provided on page 8 of the

description. It is an empirically found measure, which describes the “heat transfer” to the cell during thermal treatment. It is not known in the art. The Applicants derived this formula from a number of experiments detailed in the description, especially those in which the conditioning temperature and conditioning time were varied, and the release of metabolite, while maintaining structural integrity, was studied (see for example pages 34 and 35). From these experiments, Applicant has discovered that by keeping the difference between the culturing temperature and the conditioning temperature within a certain range, which depends on the conditioning time, maximum metabolite release is obtained with minimum loss of structural integrity.

Applicant also believes that the re-wording of claim 1 makes the nature of the invention more clear. The invention is not a “new” formula *per se*, but rather a requirement for specific choices of times and temperatures, in order achieve the objective of the invention.

5a) Claim 1 has been reworded to provide clear antecedent basis for the term “thermal equivalent”.

5b) The Examiner has objected to use of Centigrade and Kelvin in the claims. In contrast to the °F (Fahrenheit) scale, K (Kelvin) and °C (Celsius) share the same scaling, except for the zero point. Degrees C and K are commonly used in one and the same equations. It is well accepted in the field of thermodynamics that K units are used for relative values, such as heat transport, increase in temperature or in combined units like increase rate. At the same time the °C units are used to describe absolute values such as room temperature, boiling point, outlet temperature etc. The parallel use of both, °C and K in the instant claims and specification is in accordance with the use in this technical field. Conversion of °C values given to K values would impair the readability of the text and the understanding of the invention, by a person of skill in the art.

All references to time are now indicated to be in seconds (sec).

5c) The value of WE is now indicated to be in K·sec (Ks).

5d) Claim 9 has been amended to correct a clerical error such that “ t_k ” has been replaced with “ t_h ”, which appears in the formula of claim 1.

The Examiner states that “claim 1 does not contain any mathematical adjustments for the volume as noted by claim 10”. The volumetric flow value is not part of the formula of claim 1 and is not meant to be part of said formula. Rather, claim 10 further defines one physical characteristic of the liquid being flowed through the temperature-controlled segment of the capillary introduced in claim 9, by defining the volumetric flow.

5e) The preamble of claim 1 has been amended to replace “of thermal conditioning of” with “for thermally liberating an intracellular metabolite from”, providing antecedent basis for “the metabolite” found in claim 15. The term “component material” is no longer present in claim 15.

35 USC 102(b) and 103(a)

6. The Examiner finds that claims 1-11 and 15 lack novelty under 102(a) and are obvious under 103(a) in view of Lee (US, 6,197,553) for the grounds of record in the International Search Report. In particular, in the ISR, the Examiner indicated that column 3, lines 38-53, column 5, lines 10-27, claim 1, figure 1, and examples 1 and 2 were relevant. The Applicant respectfully disagrees.

As discussed in the “Background of the Invention” section of the present application, in order to recover metabolites from cells, a number of methods have been employed in the prior art. These methods involve the complete lysis of the cells, in which the cell membrane is destroyed and the component materials are released. The cell debris, naked DNA, and protein complexes are present in the cell suspension along with the desired liberated metabolites. This means that purification steps must be performed. The present inventions seeks to provide a method in which metabolites are recovered with minimal cell damage, resulting in less contamination of the metabolites with interfering materials, such as cellular debris, naked DNA, and protein complexes.

Lee et al. (US 6,197,553) (henceforth Lee) discloses the thermolysis of E. coli cells, i.e the destruction of biological cells by thermal means. Lee accomplishes this by suspending microbial cells in buffer and heating the suspension to about 70-100°C in a flow-through heat exchanger. As disclosed in Lee (e.g. see Abstract), the thermal treatment lyses the cells, and is meant to replace other techniques commonly used in the art to accomplish this, such as

alkaline lysis, lysozyme supported lysis (enzymatic digestion), and isopycnic centrifugation (see the "Background of the Invention" in columns 1 and 2 of Lee). These treatments are commonly known to result in complete lysis of the cells subjected thereto.

This is in contrast to the present invention, which expressly seeks to avoid full lysis of the cells, but rather seeks to obtain the contents from the cell, i.e. the metabolites, while avoiding contamination of the samples by the cell debris, which would be produced by full lysis.

To accomplish the goals of the present invention, the Applicants have surprisingly found that using a specific range relating the culturing temperature (T_M) the conditioning temperature (T_K), and the conditioning time (t_h), results in release of the metabolites, without complete lysis of the cells. Specifically, the present invention requires that the cells be subject to culturing and thermal conditioning steps, characterized by a thermal equivalent (WE) of 90 to 150 K·sec, in which $WE = t_h(T_K - T_M)$. In addition, the conditioning temperature (T_K) must be 80-95°C.

In contrast, Lee's examples use conditions in which the WE calculated lies outside the range required for the present invention. To support this statement, Applicant provides herewith a Declaration under 37 C.F.R. § 1.132 by Joachim Schmid. As is clearly demonstrated in this Declaration, the WE in the Examples of Lee is outside the WE range required in the present invention. In particular, the Declaration demonstrates that the WE's calculated for Lee's examples, 1651 K·s in Example 1 and 890 K·s, 352 K·s (interpolated), 243 K·s (interpolated), and 77 K·s in Example 2 (i.e. 2-a to 2-d, respectively), are not in the range of 90 to 150 K·s required for the present invention. Example 2-d is further distinguished from the present invention, in that Lee carries this example out at 65°C, whereas the present invention requires a conditioning temperature (T_K) of 80-95°C.

Thus, it is respectfully submitted that Lee does not disclose the present invention.

Furthermore, Lee cannot be said to render the present invention obvious. As is already mentioned above, Lee seeks to completely lyse the cells through thermal means. In the present invention, the goal is to release the metabolites without full lysis.

From the teaching of the Lee et al. reference it could not have been foreseen that such a technically advantageous "state of partial lysis or disintegration" as is achieved according to the present invention actually existed and/or could be used for obtaining a biological cell's contents for further analysis. Furthermore, there is no indication in Lee that such a partial disintegration could be obtained by thermal treatment. Thus, a skilled person, seeking to improve techniques for obtaining and isolating the contents of a biological cell and seeking to avoid the disadvantages of a complete cell lysis, would not find any hint or clue on how to improve or modify the Lee teachings to solve this technical problem.

Thus, it is respectfully submitted that Lee does not render obvious the present invention.

Conclusion

Reconsideration and allowance of the application is requested. Should the Examiner be of the belief that this application still does not fully comply with the Patent Act or Rules, he is urged to call the Applicant's agent, Gail Silver, at (613)787-3727.

The Commissioner is hereby authorized to debit \$130.00 from Deposit Account No. 501593, in the name of Borden Ladner Gervais LLP. The Commissioner is hereby authorized to charge any additional fees, and credit any over payments to Deposit Account No. 501593, in the name of Borden Ladner Gervais LLP.

Respectfully submitted,

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Enclosure

1.132 Declaration of Schmid

GCS/mjd